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(12) # EUROPEAN PATENT SPECIFICATION

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(54) **New cysteine derivatives having expectorant activity.**

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FR-M- 4 619

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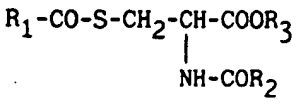
EP 0 301 474 B1

Description

It is known that N-acetylcysteine, N-propionyl-cysteine, N-caproyl-cysteine and N-benzoyl-cysteine are mucolytic agents.

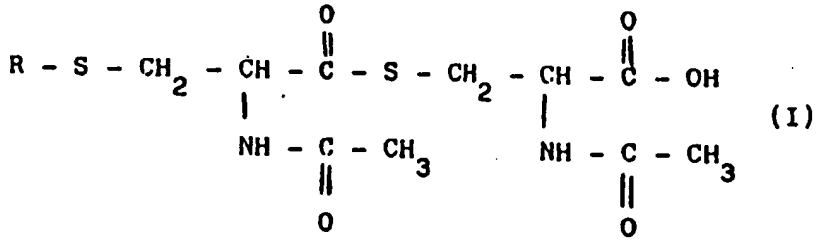
FRM 4619 discloses a class of N-acetylcysteine thioesters of general formula



wherein R_1 and R_2 are alkyl or alyl groups and R_3 is an alkyl, a cycloalkyl or an aryl radical.

These compounds with respect to N-acetylcysteine are characterized by being stable, odourless and tasteles, and moreover are soluble both in water and in organic solvent.

The present invention refers to new cysteine derivatives of the general formula (1)



(I)

in which R represents a radical of a fatty saturated or unsaturated acid, or a radical of an aromatic acid, such as benzoic, salicylic, cinnamic, 2-acetoxy-benzoic acid or of a heterocyclic acid, as well as their salts, paticularly Ca and Mg salts.

The new derivatives are excellent bronchial liquefiers and expectorants.

INVENTION FIELD

The invention refers to new cysteine derivatives having a bronchial liquefying and expectorant activity, to a process for their preparation and to pharmaceutical compositions containing them as active priciples.

DESCRIPTION

Operating according to the above referred reaction series, the starting compound for the preparation of derivatives of formula (I) according to the invention is the chloride of 3-chloro-L-alanine (II) which may be obtained from 3-chloro-L-alanine by any of the conventional methods employed for transforming an acid into its chloride, for instance by reaction with phosphorus pentachloride in a suitable solvent, such as chloroform or diethyl ether.

The chloride is obtained as a precipitate from the reaction mixture by addition of e.g. ligroin (in the ether solutions) or of diethyl ether (in the chloroform solutions). The filtered product is reacted with an excess of potassium hydrosulfide (III) to obtain the 3-chloro-L-2-amino thiopropionic acid (IV).

Compound (IV) is acetylated to obtain (VI) by any of the conventional methods employed for acylating an amino group, e.g. by reaction with acetyl chloride in a suitable solvent, such as chloroform, in the presence of an acid acceptor.

Derivative (VI) by reaction in an alkaline medium with a thio-acid (VII) provides compound (VIII), which by reaction in an alkaline medium with derivative (IX) provides derivative (I). The reaction between compound (VIII) and compound (IX) is carried out at a pH between 5 and 7 and at a temperature between 15 and 25 °C. Derivative (I) is obtained in a highly pure state by purification on a silica gel column, using as eluent chloroform-methanol (7:3).

Operating according to (b) above, an alkali salt of acetyl-3-chloroalanine (X) is reacted with ethyl chloroformate (XI) and the mixed anhydride obtained (XII) is reacted with L-acetyl-cysteine (XIII) to give

derivative (XIV); finally (XIV) by reaction in alkaline medium with the thioacid (VII), gives (I) which is purified on a silica gel column, employing as eluent a chloroform-methanol 7:3 mixture.

The reaction between compound (XII) and compound (XIII) is carried out at a pH comprised between 6 and 8 and at a temperature of between -23 and -17 °C, while the reaction of compound (XIV) with (VII) is carried out at a pH of between 5 and 7 and at a temperature of between 15 and 25 °C.

The present invention also comprises pharmaceutical compositions containing as active principles one or more of the compounds of the invention, together with pharmaceutically acceptable vehicles and diluents.

The pharmaceutical compositions may be in the following forms: solid, such as capsules, slow release or instantaneous tablets or dragees with instantaneous or delayed action, monodosis sachets; liquid, instantaneous or slow release solutions or emulsions; suppositories; solutions for injection or for instantaneous or delayed inhalation.

In the treatment of bronchial affections, the compounds according to the invention may be administered orally in posologic doses containing e.g. between 100 and 5000 mg of active substance 2-3-4 times a day; by injection and inhalation in posologic units of between 50 and 500 mg of active substance, 2-3-4 times a day; rectally in posologic units of 100 to 1000 mg of active substance 2-3-4 times a day,

The derivatives of the invention are good bronchial liquefiers and expectorants, superior to cysteine at equal doses, while showing low toxicity.

The LD_{50} value determined on mice and rats, both intraperitoneally and orally, is higher than 3000 mg/Kg for all the examined compounds.

The expectorant activity (ED_{50}), determined on rabbits according to Boyd (Boyd and Sheppard, Arch. Int. Pharm, 1966, 163, 284) is 100 mg/Kg. The same ED_{50} determined on mice according to a modified Mavatari method (Graziani, Cazzulani, Il Farmaco Ed.Prat. 1981 XXXVI, 3,167) is respectively of 37 mg/Kg.

The following examples will illustrate the process of the invention without limiting it.

EXAMPLE 1

Preparation of N-acetyl-S-(N-acetyl [(benzoyl) cysteyl) cysteine

1. Preparation of L-3-chloro-2-acetamido-thiopropanoic acid

In a 200 ml flask a solution is prepared by stirring 20 g (0.3 mol) of potassium hydroxide in 80 ml 90% ethanol.

On the flask a 50 ml separatory funnel is inserted provided with a tube through which hydrogens sulphide is introduced until the solution is saturated and it results no longer alkaline to phenophtalein,

The mixture is cooled on ice to 10-15 °C and 0.3 mol (49.3 g) and 3 chloro-L-alanine chloride-hydrochloride are added in 90 minutes while stirring at a temperature of 15 °C; the reaction is then stirred for an additional hour.

The potassium chloride which is formed is filtered off, washed with 20 ml 95% ethanol, the solutions are collected and ethanol is evaporated under reduced pressure.

The solid residue is dissolved in 70 ml of cold water and the solution is filtered.

0.3 mol acetyl chloride are then added slowly, under strong stirring and under control of the pH, which should be about 8.

The solution is stirred for an additional hour and acidified pH 2.0 with hydrochloric acid.

The formed precipitate is filtered off, washed with water and dried in an oven. The dry product is crystallised from water.

15 g of product are obtained.

The structure is confirmed by spectral analyses.

Elemental analysis	C	H	Cl	N	S
- Calculated	33,06%	4,43%	19,50%	7,71%	17,65%
- Found	33,5%	4,5%	19,3%	7,7%	17,5%
- M.W 181.63					

2. Preparation of L-3-benzoyl mercapto-2-acetamido thiopropanoic acid.

54.3 g (0.3 mol) of L-3-chloro-2-acetamido-thiopropanoic acid are suspended in 150 ml of water brought to pH 5.0 by addition of sodium hydroxyde. The temperature is brought to 20 °C and 46 g thiobenzoic acid, 24 g anhydrous potassium carbonate and 300 ml water are added rapidly. A yellow, almost clear solution is obtained at pH 6.06 which is left overnight (in the darkness) at about 18 °C.

Thereafter 21 mol 35% hydrochloric acid are added slowly under pH control until a stable pH of 4.0 is reached.

The formed precipitate is filtered on a Büchner funnel and washed with 4x100 ml water.

The product is then dried in an oven

Approximately 80 g of product are obtained. The structure is confirmed by spectral analyses.

Elemental analysis	C	H	N	S
- Calculated	51,14%	5,07%	5,42%	24,85%
- Found	51,2%	5,04%	5,44%	24,7%
- M.W. 258.347				

3. Preparation of N-acetyl-S-(N-acetyl[(benzoyl) cysteyl)cysteine

49.69 g (0.3 mol) 3-chloro-N-acetyl-alanine are suspended in 150 ml of water, which is then brought to pH 5.0 by adding sodium hydroxide. The temperature is brought to 20 °C and 78.5 g of L-3-benzoyl mercapto - 2-acetamido-thiopropanoic acid, 24 g anhydrous potassium carbonate and 300 ml water are rapidly added.

A yellow almost clear solution is obtained at a pH of 6.06 which is left for one right at 18 °C, in the darkness.

Thereafter 35% hydrochloric acid is added slowly, under pH control, to a stable pH to 4.0.

The precipitate is filtered off, washed with 4x100 ml water and dried in an oven. 120 g of a product are obtained which can be purified by dissolution it in ethyl acetate and reprecipition by addition of ligroin or ethyl ether.

The structure is confirmed by spectral analysis.

Elemental analysis	C	H	N	S
- Calculated	51,36%	5,277%	7,046%	16,13%
- Found	51,4%	5,28%	7,1%	16,2%
- MW. 397.49				

EXAMPLE 2

Preparation of N-acetyl-s-(N-acetyl cysteyl)cysteine

1. Preparation of N-acetyl-s-(N-acetyl-3-chloro-alanyl) cysteine

Suspension A

In a 4 neck 2 liter flask provided with stirrer, thermometer, calcium chloride protection tube, 67.20 g (0.330 mol) of finely powdered potassium salt of N-acetyl-3-chloro-L-alanine and 600 ml acetone are introduced. After cooling to 20 °C 33.6 g ethyl chloroformate and 26 mol N-methyl morpholine are added. The suspension is left standing for two hours at a temperature of 10 °C or lower, and it is then brought to 30°C.

Solution B

50 g (0,276 mol) of N-acetyl-cysteine, 70 ml acetone and 25 g triethylamine are placed into a 400 ml beaker while stirring and under pH control in such a way that the pH does not rise above 7.5.

The solution is then cooled to 0/-3 °C.

Reaction

Solution B is added to suspension A under stirring within a few minutes keeping the temperature at -15 °/-20 °C.

The turbid solution is kept at -15 °/-20 °C for three hours under stirring, then the temperature is raised to 0 °C and the stirring is continued for additional 4 hours.

170 ml of water are then added and the solution is placed into a 2 liter beaker. It has a pH of approximately 6,25.

Keeping the temperature at between 0 ° and 5 °C, hydrochloric acid is added to a constant pH of 4.0.

The solution is extracted with 1000 ml methylene chloride.

The precipitate which is formed is filtered off and washed with 4x100 ml of water. It is then dried in an oven obtaining 70 g of product.

The structure is confirmed by spectral analysis.

Elemental analysis	C	H	N	S	Cl
- Calculated	38,09%	5,656%	9,871%	11,299%	12,495%
- Found	38,2%	5,66%	9,88%	11,25%	12,4%
- M.W. 283.74					

2. (Preparation of N-acetyl-s-(N-acetyl-cysteyl)cysteine

In a 200 ml flask a solution of 20 g (0.3 mol) of potassium hydroxide in 80 nil 90% ethanol is prepared. On the flask a 50 ml separatory funnel is inserted provided with a tube through which hydrogen sulphide is introduced until the solution is saturated and it results no longer alkaline to phenolphtalein.

The mixture is cooled on ice to 10-15 °C and 0.3 mol (85.12g) of N-acetyl-s-(N-acetyl-3-chloro alanyl) cysteine are added.

The mixture is heated or reflux for two hours.

After cooling and filtration, the filtrate is diluted with 100ml water.

The pH is brought to 4.0. The obtained precipitate is filtered off, washed with water and oven dried.

Approximately 75g of product are obtained.

The structure is confirmed by instrumental analysis

Elemental analysis	C	H	N	S
- Calculated	38,95%	5,198%	9,083%	20,79%
- Found	38,9%	5,2%	9,1%	20,2%
- M.W. 308.37				

EXAMPLE 3

Preparation of N-acetyl-s-(N-acetyl[(benzoyl)cysteyl]cysteine

Thiobenzoic acid is reacted with N-acetyl-s-(N-acetyl-3-chloro-alanyl)cysteine

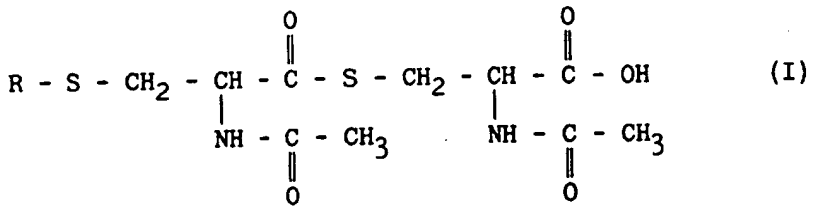
EXAMPLE 4

The derivatives obtained in the preceding examples are treated with $Ca(OH)_2$ to obtain the respective salts.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, LU, NL, SE

1. Cysteine derivatives of the general formula (I)



(I)

wherein R represents H or the radical of a saturated or unsaturated fatty acid, or of an aromatic acid such as benzoic, cynnamic, salicylic, 2-acetoxybenzoic acid, or of a heterocyclic acid, and their therapeutically active salts, in particular Ca and Mg salts.

2. N-acetyl-S-(N-acetyl cysteyl) cysteine.

3. N-acetyl-S-{N-acetyl-3-[(benzoyl) cysteyl]} cysteine.

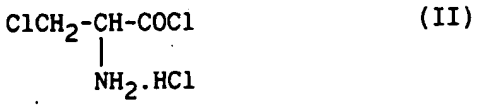
4. N-acetyl-S-{N-acetyl-3-[(2-acetoxybenzoyl) - cysteyl]} cysteine.

5. N-acetyl-S-{N-acetyl-3-[(cynnamoyl)-cysteyl]} cysteine.

6. N-acetyl-S-{N-acetyl-3-[(2-oxybenzoyl) cysteyl]} cysteine.

7. A process for preparing the cystein derivatives according to claim 1 characterized in that it comprises the following steps:

(a) reacting 3-chloro-L-alanine chloride hydrochloride of formula (II)

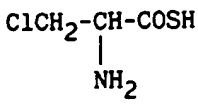


(II)

with an excess of potassium hydrosulphide (III)

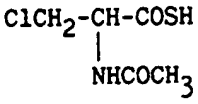
KSH (III)

thereby obtaining 3-chloro-L-2-amino thiopropionic acid (IV):



(IV)

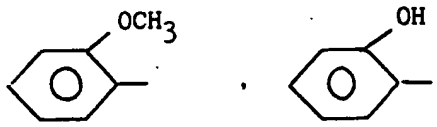
(b) reacting compound (IV) with acetylchloride (V) CH_3-COCl thereby obtaining the derivative (VI)



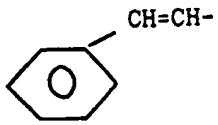
(c) reacting (VI) in an alkaline medium with a thioacid (VII)

R'-COSH (VII)

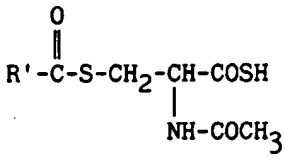
wherein R' is phenyl,



a heterocyclic ring

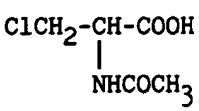


or a saturated or an unsaturated alkyl residue of a fatty acid thereby obtaining the compound (VIII)



(VIII)

(d) reacting the compound (VIII) with the derivative of formula (IX)

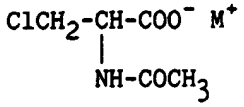


(IX)

at pH comprised between 5 and 7 at a temperature between 15 and 25 °C, thereby obtaining the compound of formula (I).

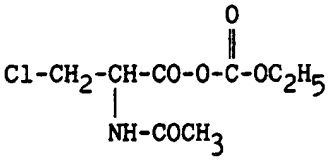
8. A process for preparing the cysteine derivative of formula (I) according to claim 1, characterized in that it comprises the following steps:

a) an alkali salt of acetyl-3-chloroalanine of formula (X)



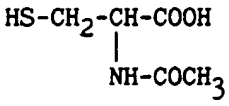
(X)

wherein M^+ is a metal alkali cation
is reacted with
ClCOOEt (XI) thereby obtaining the mixed anhydride (XII)



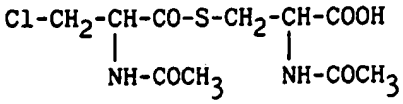
(XII)

b) the compound (XII) is reacted with L-acetylcysteine (XIII)



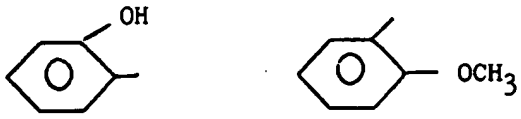
(XIII)

at a pH comprised between 6 and 8 and at a temperature comprised between -23 and -17 °C thereby obtaining (XIV)

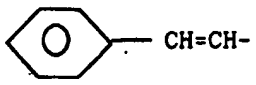


(XIV)

c) the compound (XIV) is reacted at pH of between 5 and 7 and at a temperature of between 15 and 25 °C with the compound R'COSH (VII) wherein R' is a saturated or unsaturated alkyl residuo of a fatty acid,
or is phenyl,



a heterocyclic ring, or



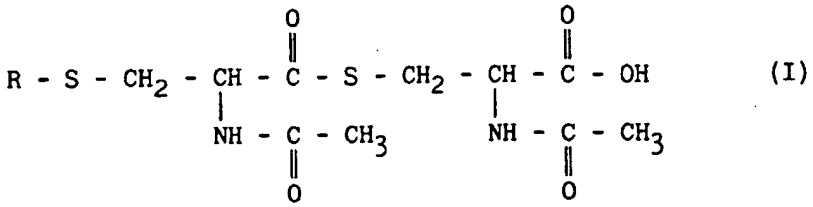
thereby obtaining the compound of formula (I).

9. The process according to claim 8 characterized in that in step (a) the potassium salt of the compound of formula (X) is used.

10. Pharmaceutical preparation administrable by injection, by aerosol or by oral or rectal way, having expectorant and liquefying bronchial action, characterized by containing as active principles derivatives according to claims 1 to 6.

Claims for the following Contracting States : ES, GR

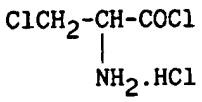
1. A process for preparing cysteine derivatives having expectorant and liquefying bronchial action of the general formula (I):



(I)

wherein R represents H or the radical of a saturated or unsaturated fatty acid, or of an aromatic acid such as benzoic, cynnamic, salicylic, 2-acetoxybenzoic acid, or of a hetero-cyclic acid, and their therapeutically active salts, in particular Ca and Mg salts, characterized in that it comprises the following steps:

(a) reacting 3-chloro-L-alanine chloride hydrochloride of formula (II)

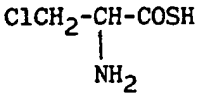


(II)

with an excess of potassium hydrosulphide (III)

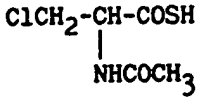
KSH (III)

thereby obtaining 3-chloro-L-2-amino thiopropionic acid (IV):



(IV)

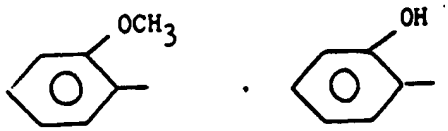
(b) reacting compound (IV) with acetylchloride (V) CH_3-COCl thereby obtaining the derivative (VI)



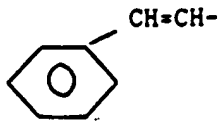
(c) reacting (VI) in an alkaline medium with a thioacid (VII)

R'-COSH (VII)

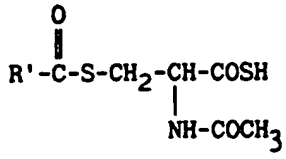
wherein R' is phenyl,



a heterocyclic ring

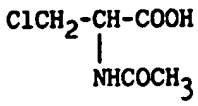


or a saturated or an unsaturated alkyl residue of a fatty acid
thereby obtaining the compound (VIII)



(VIII)

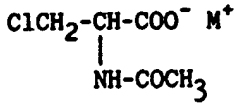
(d) reacting the compound (VIII) with the derivative of formula (IX)



(IX)

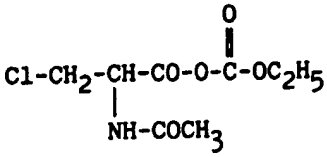
at pH comprised between 5 and 7 at a temperature between 15 and 25 °C, thereby obtaining the compound of formula (I),
or alternatively characterized in that it comprises the following steps:

a') an alkali salt of acetyl-3-chloroalanine of formula (X)



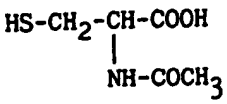
(X)

wherein M^+ is a metal alkali cation
is reacted with
ClCOOEt (XI) thereby obtaining the mixed anhydride (XII)



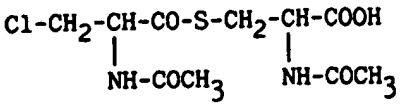
(XII)

b') the compound (XII) is reacted with L-acetylcysteine (XIII)



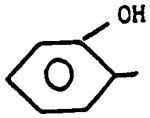
(XIII)

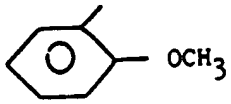
at a pH comprised between 6 and 8 and at a temperature comprised between -23 and -17 °C thereby obtaining (XIV)



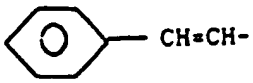
(XIV)

c') the compound (XIV) is reacted at pH of between 5 and 7 and at a temperature of between 15 and 25 °C with the compound R'COSH (VII) wherein R' is a saturated or unsaturated alkyl residuo of a fatty acid,
or is phenyl,





a heterocyclic ring, or



thereby obtaining the compound of formula (I).

2. The process according to claim 1, wherein said cysteine dervivative is N-acetyl-S-(N-acetyl cysteyl) cysteine.

3. The process according to claim 1, wherein said cysteine derivative is N-acetyl-S-{N-acetyl-3-[(benzoyl) cysteyl)} cysteine.

4. The process according to claim 1, wherein said cysteine derivative is N-acetyl-S-{N-acetyl-3-[(2-acetoxybenzoyl) - cysteyl]} cysteine.

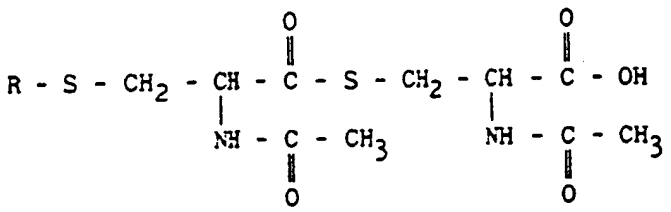
5. The process according to claim 1, wherein said cysteine derivative is N-acetyl-S-{N-acetyl-3-[-(cynnamoyl)-cysteyl]} cysteine.

6. The process according to claim 1, wherein said cysteine derivative is N-acetyl-S-{N-acetyl-3-[(2-oxybenzoyl)cysteyl]}cysteine.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Cystein-Derivate der allgemeinen Formel (I)



(I)

worin R H oder das Radikal einer gesättigten oder ungesättigten Fettsäure oder einer aromatischen Säure, wie Benzoesäure, Zimtsäure, Salicylsäure, 2-Acetoxybenzoesäure oder einer heterocyclischen Säure darstellt, und deren therapeutisch aktive Salze, insbesondere Ca- und Mg-Salze.

2. N-Acetyl-S-(N-acetylcysteyl)-cystein.

3. N-Acetyl-S-{N-acetyl-3-[(benzoyl)-cysteyl]}-cystein.

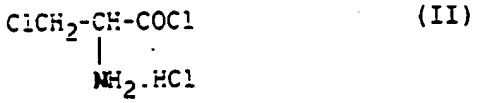
4. N-Acetyl-S-{N-acetyl-3-[(2-acetoxybenzoyl)-cysteyl]}-cystein.

5. N-Acetyl-S-{N-acetyl-3-[(cinnamoyl)-cysteyl]}-cystein.

6. N-Acetyl-s-{N-acetyl-3-[(2-oxybenzoyl)-cysteyl]}-cystein.

7. Verfahren zur Herstellung der Cystein-Derivate gemäß Anspruch 1, dadurch **gekennzeichnet**, daß es die folgenden Schritte umfaßt:

(a) Umsetzen von 3-Chloro-L-alaninchlorid-hydrochlorid der Formel (II)

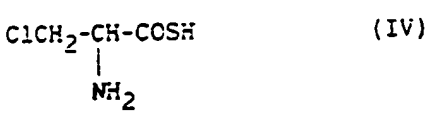


(II)

mit einem Überschuß an Kaliumhydrogensulfid (III)

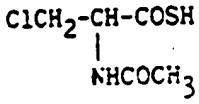
KSH (III)

wodurch 3-Chloro-L-2-aminothiopropionsäure (IV) erhalten wird:



(IV)

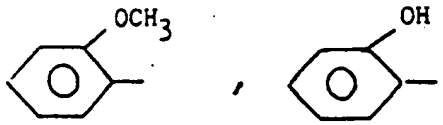
(b) Umsetzen von Verbindung (IV) mit Acetylchlorid (V) CH_3-COCl, wodurch das Derivat (VI) erhalten wird



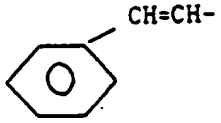
(c) Umsetzen von (VI) in alkalischem Medium mit einer Thiosäure (VII)

R'-COSH (VII)

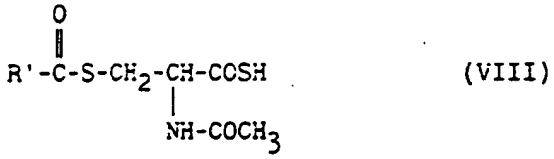
worin R' Phenyl,



ein heterocyclischer Ring

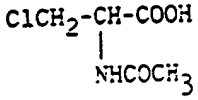


oder ein gesättigter oder ungesättigter Alkylrest einer Fettsäure ist, wodurch die Verbindung (VIII) erhalten wird



(VIII)

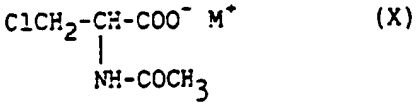
(d) Umsetzen der Verbindung (VIII) mit dem Derivat der Formel (IX)



(IX)

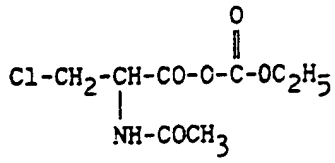
bei einem pH zwischen 5 und 7 und bei einer Temperatur zwischen 15 und 25 °C, wodurch die Verbindung der Formel (I) erhalten wird.

8. Verfahren zur Herstellung des Cystein-Derivats der Formel (I) gemäß Anspruch 1, dadurch **gekennzeichnet**, daß es die folgenden Schritte umfaßt:
a) ein Alkalisalz von Acetyl-3-chloroalanin der Formel (x)



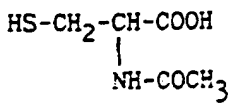
(X)

worin M^+ ein Alkalimetallkation ist, wird umgesetzt mit ClCOOEt (XI), wodurch das gemischte Anhydrid (XII)



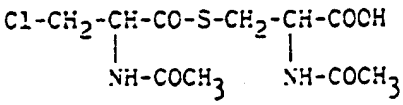
(XII)

erhalten wird,
b) die Verbindung (XII) wird umgesetzt mit L-Acetylcystein (XIII)



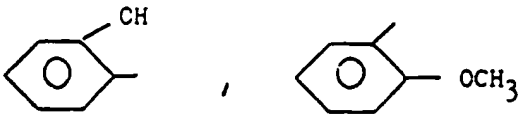
(XIII)

bei einem pH zwischen 6 und 8 und einer Temperatur zwischen -23 und -17 °C wodurch (XIV) erhalten wird

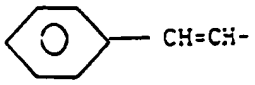


(XIV)

c) die Verbindung (XIV) wird bei einem pH zwischen 5 und 7 und einer Temperatur zwischen 15 und 25 °C mit der Verbindung R'COSH (VII) umgesetzt, worin R' ein gesättigter oder ungesättigter Alkylrest einer Fettsäure, oder Phenyl,



ein heterocyclischer Ring oder



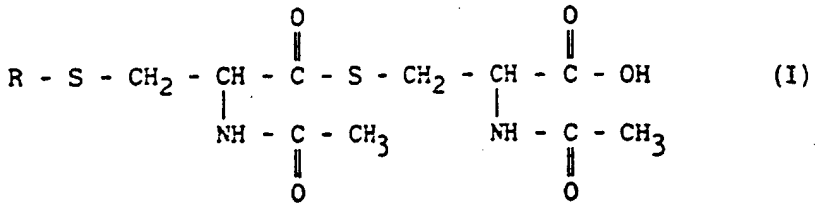
ist, wodurch die Verbindung der Formel (I) erhalten wird.

9. Verfahren gemäß Anspruch 8, dadurch **gekennzeichnet**, daß in Schritt (a) das Kaliumsalz der Verbindung der Formel (X) verwendet wird.

10. Pharmazeutische Zubereitung, verabreichbar durch Injektion durch Aerosol oder auf oralem oder rektalem Weg mit Expektorans-Wirkung und bronchialverflüssigender Wirkung, dadurch **gekennzeichnet**, daß sie als aktives Prinzip Derivate gemäß den Ansprüchen 1 bis 6 enthält.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung von Cystein-Derivaten mit Expektorans-Wirkung und bronchialverflüssigender Wirkung der allgemeinen Formel (I):

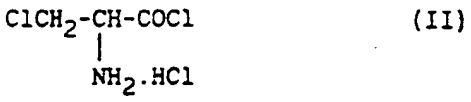


(I)

worin R H oder das Radikal einer gesättigten oder ungesättigten Fettsäure oder einer aromatischen Säure wie Benzoesäure, Zimtsäure, Salicylsäure, 2-Acetoxybenzoesäure, oder einer heterocyclischen Säure darstellt, und deren therapeutisch aktive Salze, insbesondere Calcium- und Magnesiumsalze, dadurch **gekennzeichnet**, daß es die folgenden Schritte umfaßt:

(a) Umsetzen von

3-Chloro-L-alanininchlorid-hydrochlorid der Formel (II)



(II)

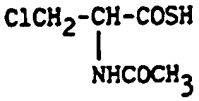
mit einem Überschuß Kaliumhydrogensulfid (III)

KSH (III)

wodurch 3-Chloro-L-2-aminothiopropionsäure (IV) erhalten wird

(IV)

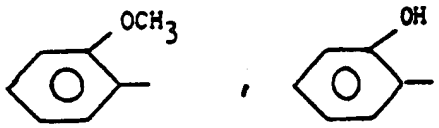
(b) Umsetzen von Verbindung (IV) mit Acetylchlorid (V) CH_3-COCl, wodurch das Derivat (VI) erhalten wird



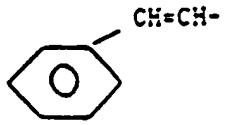
(c) Umsetzen von (VI) in alkalischem Medium mit einer Thiosäure (VII)

R'-COSH (VII)

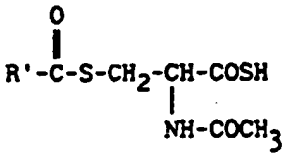
worin R' Phenyl,



ein heterocyclischer Ring

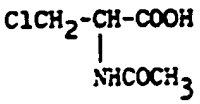


oder ein gesättigter oder ungesättigter Alkylrest einer Fettsäure ist, wodurch die Verbindung (VIII) erhalten wird



(VIII)

(d) Umsetzen der Verbindung (VIII) mit dem Derivat der Formel (IX)

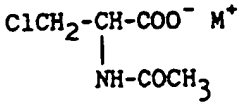


(IX)

bei einem pH zwischen 5 und 7 und einer Temperatur zwischen 15 und 25 °C, wodurch die Verbindung der Formel (I) erhalten wird, oder alternativ

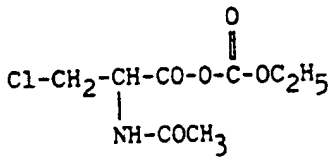
gekennzechnet dadurch, daß er die folgenden Schritte umfaßt:

a') ein Alkalisalz von Acetyl-3-chloroalanin der Formel (X)



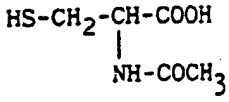
(X)

worin M^+ ein Alkalimetallkation ist, wird umgesetzt mit ClCOOEt (XI), wodurch das gemischte Anhydrid (XII) erhalten wird



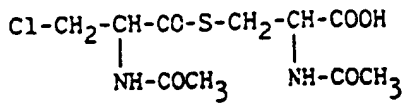
(XII)

b') die Verbindung (XII) wird umgesetzt mit L-Acetylcystein (XIII)



(XIII)

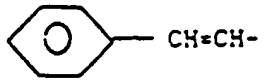
bei einem pH zwischen 6 und 8 und einer Temperatur zwischen -23 und -17 °C, wodurch (XIV) erhalten wird



(XIV)

c') die Verbindung (XIV) wird bei einem pH zwischen 5 und 7 und einer Temperatur zwischen 15 und 25 °C mit der Verbindung R'COSH (VII) umgesetzt, worin R' ein gesättigter oder ungesättigter Alkylrest einer Fettsäure, Phenyl,

ein heterocyclischer Ring oder



ist, wodurch die Verbindung der Formel (I) erhalten wird.

2. Verfahren gemäß Anspruch 1, dadurch **gekennzeichnet**, daß das Cystein-Derivat N-Acetyl-S-(N-acetylcysteyl)-cystein ist.

3. Verfahren gemäß Anspruch 1, worin das Cystein-Derivat N-Acetyl-S-{N-acetyl-3-[(benzoyl)cysteyl]}-cystein ist.

4. Verfahren gemäß Anspruch 1, dadurch **gekennzeichnet**, daß das Cystein-Derivat N-Acetyl-S-{N-acetyl-3-[(2-acetoxybenzoyl)-cysteyl]}-cystein ist.

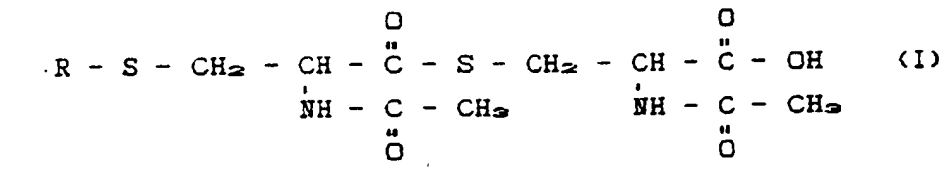
5. Verfahren gemäß Anspruch 1, dadurch **gekennzeichnet**, daß das Cystein-Derivat N-Acetyl-S-{N-acetyl-3-[(cinnamoyl))cysteyl]}-cystein ist.

6. Verfahren gemäß Anspruch 1, dadurch **gekennzeichnet**, daß das Cystein-Derivat N-Acetyl-S-{N-acetyl-3-[(2-oxybenzoyl)cysteyl]}-cystein ist.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Dérivés de cystéine de formule générale (I)



(I)

dans laquelle R représente H ou le radical d'un acide gras saturé ou insaturé, d'un acide aromatique tel que l'acide benzoïque, cinnamique, salicylique, 2-acétoxybenzoïque ou d'un acide hétérocyclique, et leurs sels thérapeutiquement actifs, en particulier leurs sels de Ca et de Mg.

2. N-acétyl-S-(N-acetylcystéyl)cystéine.

3. N-acétyl-S-{N-acetyl-3-[(benzoyl)cystéyl]}-cystéine.

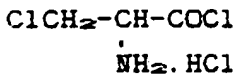
4. N-acétyl-S-{N-acétyl-3-[(2-acétoxybenzoyl)-cystéyl]}cystéine.

5. N-acétyl-S-{N-acétyl-3-[(cinnamoyl)cystéyl]}-cystéine.

6. N-acétyl-S-{N-acétyl-3-[(2-oxybenzoyl)cystéyl]}-cystéine.

7. Procedé de préparation des dérivés de cystéine selon la revendication 1, caractérisé en ce qu'il comprend les étapes consistant

(a) à faire réagir du chlorhydrate de chlorure de 3-chloro-L-alanine de formule (II)

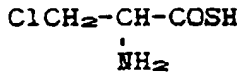


(II)

avec un excès d'hydrogénosulfure de potassium (III)

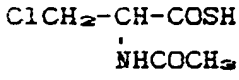
KSH (III)

de façon à obtenir de l'acide 3-chloro-L-2-aminothio-propionique (IV)



(IV)

(b) à faire réagir le composé (IV) avec du chlorure d'acétyle (V) CH_3-COCl, de façon à obtenir le dérive (VI)

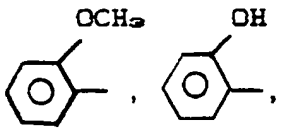


(VI)

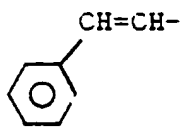
(c) a faire réagir le dérivé (VI) dans un milieu alcalin avec un thio-acide (VII)

R'-COSH (VII)

dans laquelle R' est un reste phényle,

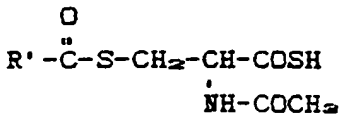


un noyau hétérocyclique,



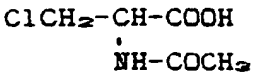
ou un résidu alkyle saturé ou insaturé d'un acide gras,

de façon à obtenir le composé (VIII)



(VIII)

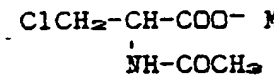
(d) à faire réagir le composé (VIII) avec le dérivé de formule (IX)



(IX)

à un pH compris entre 5 et 7 et à une température entre 15 et 25 °C, de façon à obtenir le composé de formule (I).

8. Procédé de préparation du dérivé de cysteine de formule (I) selon la revendication 1, caractérisé en ce qu'il comprend les étapes suivantes:
(a) un sel alcalin d'acétyl-3-chloroalanine de formule (X)

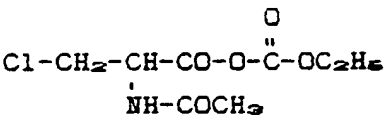


(X)

dans laquelle M^+ est un cation de métal alcalin est mis en réaction avec

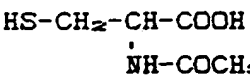
ClCOOEt (XI)

de façon à obtenir l'anhydride mixte (XII)



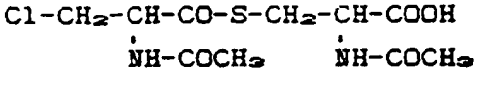
(XII)

(b) le composé (XII) est mis en réaction avec de la L-acétylcystéine (XIII)



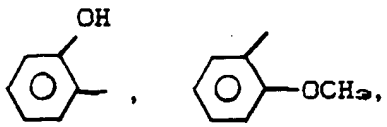
(XIII)

à un pH compris entre 6 et 8 et à une température comprise entre -23 et -17 °C, de façon à obtenir (XIV)

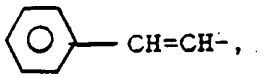


(XIV)

(c) le composé (XIV) est mis en réaction, à un pH de 5 à 7 et à une température de 15 à 25 °C, avec le composé R'COSH (VII), dans lequel R' est un residu alkyle saturé ou insaturé d'un acide gras ou est un reste phényle,



un noyau hétérocyclique ou



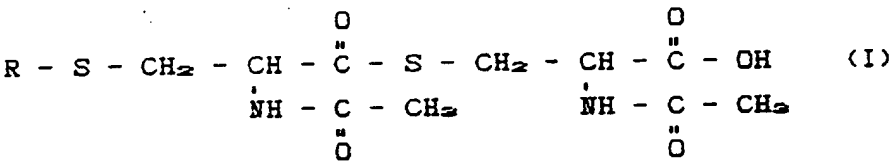
de façon à obtenir le composé de formule (I).

9. Procédé selon la revendication 8, caractérisé en ce qu'on utilise, dans l'étape (a), le sel potassique du composé de formule (X).

10. Préparation pharmaceutique administrable par injection, par aérosol ou par voie orale ou rectale, dotée d'une activité expectorante et fluidifiante des secrétions bronchiques, caractérisée en ce qu'elle contient, comme ingrédients actifs, des dérivés selon l'une quelconque des rebendications 1 à 6.

Revendications pour les Etats contractants suivants : ES, GR

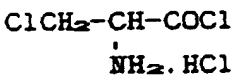
1. Procédé de préparation de dérivés de cystéine dotés d'activité expectorante et fluidifiante des sécrétions bronchiques, de formule générale (I)



(I)

dans laquelle R représente H ou le radical d'un acide gras saturé ou insaturé, d'un acide aromatique tel que l'acide benzoïque, cinnamique, salicylique, 2-acétoxybenzoïque ou d'un acide hétérocyclique, ainsi que de leurs sels thérapeutiquement actifs, en particulier leurs sels de Ca et de Mg, caractérisé en ce qu'il comprend les étapes consistant

(a) à faire réagir du chlorhydrate de chlorure de 3-chloro-L-alanine de formule (II)

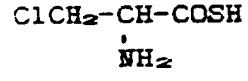


(II)

avec un excès d'hydrogénosulfure de potassium (III)

KSH (III)

de façon à obtenir de l'acide 3-chloro-L-2-aminothiopropionique (IV)



(IV)